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Review

Tuberculosis and chronic respiratory disease: a systematic review

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ABSTRACT

Background: Chronic respiratory disease causes substantial global morbidity and mortality. The contribution of pulmonary tuberculosis to the aetiology of chronic respiratory disease is rarely considered, but may be important in tuberculosis-endemic areas.
Methods: We performed a systematic literature review to assess the association between a history of tuberculosis and the presence of chronic obstructive pulmonary disease (COPD) or chronic suppurative lung disease (bronchiectasis). Study quality was evaluated using the National Heart Lung and Blood Institute quality assessment tool. Meta-analysis was performed using the DerSimonian and Laird random effects model.
Results: We identified 9 eligible studies for COPD and 2 for bronchiectasis. Overall, there was a significant association between a history of tuberculosis and the presence of COPD in adults aged over 40 years (pooled odds ratio 3.05 (95% confidence interval 2.42, 3.85). Among individual COPD studies the strongest associations were found in countries with a high incidence of tuberculosis, as well as among never smokers and younger people.
Conclusion: In tuberculosis endemic areas, tuberculosis is strongly associated with the presence of chronic respiratory disease in adults. Efforts to improve long-term lung health should be part of tuberculosis care.

1. Introduction

Economic development has been associated with a pronounced epidemiological transition, resulting in a decreased burden of infectious diseases, but a greatly increased burden of non-communicable diseases (NCDs)[1]. While the epidemiologic transition is in progress, as it is in many low- and middle-income countries, people face the double burden of infectious diseases and non-communicable diseases [2]. Bidirectional associations exist between "old' infectious diseases and "new" non-communicable ones [3]. Tuberculosis (TB) is an important case in point.

Since *M. tuberculosis* is spread by aerosol droplets, the lungs are most commonly affected by the disease [4,5]. It is well known that environmental exposures, such as silica dust or cigarette smoke, increase the risk of developing TB [6–8]. Diabetes, a non-communicable disease of growing importance, has also been shown to increase the risk of progression to active TB [9,10]. Conversely, it is now becoming clearer that TB itself may lead to chronic respiratory disease, particularly bronchiectasis and COPD [11,12]. The population attributable risk for COPD due to cigarette smoking varies from more than 70% in some high income countries to less than 40% in low and middle income countries [13]. The other factors that cause COPD in low and middle income countries have not been established, but TB may well play an important role [14].

Many low and middle-income countries are undergoing changes that actually increase TB risk, such as rapid urbanization with high population densities and increased rates of cigarette

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smoking [15]. In China alone it is estimated that 320 million people are current smokers, including 57% of all adult males, and if these rates do not decrease then the number of smoking-related deaths in that country will double to an estimated 2 million per year by 2020 [16,17]. The poor and socially destitute are particularly at risk, due to an increased risk of acquiring *Mycobacterium tuberculosis* infection in crowded living conditions and a greater vulnerability to progress to active disease because of co-morbid conditions [5,18]. TB occurred in an estimated 9 million people in 2013 [4]. This represents a large population at-risk of adverse lung health outcomes, especially if exposed to additional pulmonary insults.

Chronic respiratory disease is a group of disorders that primarily affect the lungs and airways. It is associated with significant morbidity and mortality[19]. The World Health Organization (WHO) estimates that 4.6 million people die prematurely each year as a result of chronic respiratory disease, accounting for more than 5% of global deaths; almost 90% of these occur in low and middle-income countries [20]. The 2010 global burden of disease report ranked COPD as the 9th leading cause of disability worldwide and this is predicted to rise to 5th by 2020 [21]. In adults COPD is the most common chronic respiratory disease and bronchiectasis is another debilitating airway disease that shares some clinical features but is often under recognised [22,23]. It is characterized by persistent airway dilation and a chronic productive cough [24], leading to repeated respiratory infections, deterioration in lung function and reduced quality of life [25,26].

This systematic review examines the available evidence on the association between TB and chronic respiratory disease, with a focus on COPD and bronchiectasis. The primary review questions were,"In the general population is a previous episode of TB associated with COPD or chronic suppurative lung disease (bronchiectasis)?"

2. Methods

We performed a systematic review of the literature in accordance with PRISMA guidelines [27]. The electronic databases of Medline (Web of Science) and the Cochrane library were screened for articles that contained the terms [28] "tuberculosis" or "respiratory tract disease". The search then focused specifically on "obstructive" lung disease or "bronchiectasis" (Figure 1). Studies relating to reactive airway disease (asthma) and the parenchymal lung diseases, including pneumoconiosis (silicosis, coal miner's pneumoconiosis, and asbestosis) and other causes of pulmonary fibrosis, were not considered. Articles were limited to human studies published between January 1975 and September 2014. No language restrictions were applied. All articles identified by the initial search were reviewed by title and abstract for relevance (by ALB). Duplicates, non-human studies and off-topic articles were excluded. Narrative reviews, case reports and case series were also excluded.

Studies that recruited participants from the general population, including population-based cohort, cross-sectional or nested case-control studies were included. Full-text of the included studies was assessed using a standard data collection form, documenting study setting, study design and participant selection, TB definition, COPD/bronchiectasis definition, key findings including hazard or odds ratio, key limitations and follow up period. Two authors (ALB & CDM) applied the National Heart Lung and Blood Institute (NHLBI) quality assessment tool for observational cohort and cross-sectional studies to assess the internal validity and risk of bias for each study [29]. They independently evaluated the components of the scale as "Yes", "No" "Not Applicable" or "Not Recorded". This was used to guide the overall rating for the quality of each study as "Good", "Fair" or "Poor". In case of disagreement a consensus opinion was reached.

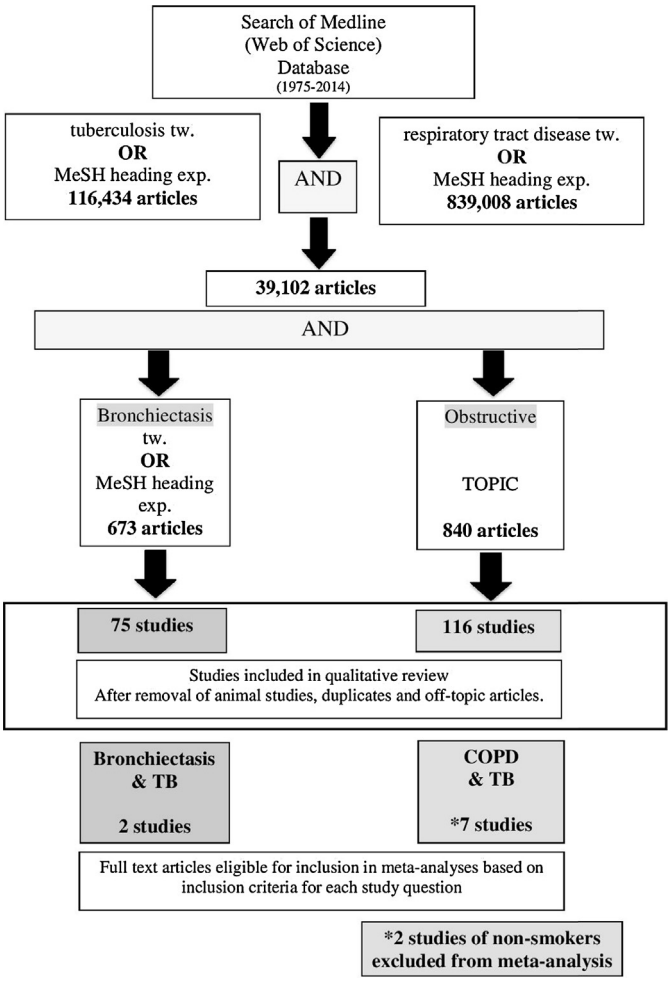

Figure 1. Flow diagram demonstrating search strategy used.
COPD excluded studies included **45** studies assessing lung function loss in TB patients (case series), **28** studies on biomass fuel or smoking, **8** studies the risk of TB infection with corticosteroid treatment for COPD, **11** studies on silicosis or pneumoconiosis and **4** studies that looked at the increased risk of lung cancer following pulmonary tuberculosis infection.
Bronchiectasis excluded studies included **22** on haemoptysis, **10** on non-tuberculosis mycobacteria, **6** narrative reviews and **25** that described bronchiectasis in select TB sub-populations.
tw.: Text words used in addition to MeSH;
TB: tuberculosis, mycobacterium tuberculosis, TB, mycobacterial infection, TBC
COPD: chronic respiratory disease, chronic lung disease, chronic obstructive lung disease, COPD, chronic airway limitation, CAL, lung disorder, asthma, obstructive lung function, lung function, spirometry, pulmonary function testing.
Bronchiectasis bronchiectasis, chronic suppurative lung disease
MeSH exp.: Medical Subject Heading expanded to include all sub-headings; Tuberculosis, Respiratory Tract Diseases, Bronchiectasis, Pulmonary Disease, Chronic Obstructive.

2.1. Meta-analysis

Odds ratios and hazard ratios for TB and chronic respiratory disease, and their associated standard errors, were log-transformed and then a random effects meta-analysis was performed in accordance with the method of DerSimonian and Laird [30]. This was implemented in SAS 9.3 (SAS Institute, Cary NC) using the *marandom* macro of Senn et al., [31]. A forest plot was created using the same authors' *maforest* SAS macro. The combined odds ratio was estimated as the exponent of the resulting meta-analytic estimate. Heterogeneity was assessed by Cochrane's Q and the I^2 statistic [32].

Table 1
Characteristics of all studies included in qualitative analysis.

COPD Studies:	Design	Setting	Follow Up (Cohort studies)	Definition Tuberculosis	Definition Outcome
Hooper 2012	Cross-sectional	BOLD (14 countries)	n/a	Past TB history	"Modified" ≥GOLD 1 (Fev1/FVC < LLN)
Perez 2012	Cross -sectional	PLATINO (Latin America)	n/a	Past TB history	≥GOLD 2
Lee 2012	Cohort (Nested)	Taiwan	> 4 years	Recorded TB treatment	Recorded COPD treatment
Idolor 2011	Cross-sectional	Philippines	n/a	Past TB history	≥GOLD 1
Lee 2011	Cross-sectional	Korea	n/a	Abnormal CXR	≥GOLD 1 (Pre-bronchodilator)
Lamprecht 2011	Cross-sectional	BOLD (14 countries)	n/a	Past TB history	≥GOLD 2
Caballero 2008	Cross-sectional	Colombia	n/a	Past TB history	≥GOLD 2
Menezes 2007	Cross-sectional	PLATINO (Latin America)	n/a	Past TB history	≥GOLD 1
Ehrilich 2005	Cross-sectional	South African	n/a	Past TB history	Clinical COPD
Bronchiectasis Studies:					
Zhou 2013	Cross-sectional	China	n/a	Past TB history	Clinical Bronchiectasis
Kwak 2010	Cross-sectional	Korea	n/a	Past TB history	CT Bronchiectasis

n/a: not applicable
GOLD 1: Grade 1 COPD defined by the Global Initiative for Obstructive Lung Disease as a ratio of Forced Expiratory Volume in 1 second (FEV1) to Forced Vital Capacity (FVC) of less than 70% following the administration of bronchodilator (usually 200-400mcg of inhaled salbutamol).
GOLD 2: Grade 2 COPD defined as an FEV1 of between 50 and 80% of predicted as well as an FEV1/FVC ratio of less than 70% following bronchodilator.
LLN: Lower Limit of Normal (of the predicted ratio rather than the GOLD definition of 70%).

3. Results

Figure 1 presents a flow diagram of the literature search results. We identified 39,102 articles using the search terms "tuberculosis" or "respiratory tract disease". The additional search term "obstructive", identified 840 articles relevant to COPD, but only 9 studies fulfilled our inclusion criteria by assessing the prevalence of COPD among the general population with and without a defined history of previous tuberculosis [33–41]. Two studies that examined data from a sub-group of never-smokers (defined as less than 20 packets of cigarettes smoked throughout the subjects entire life or less than 1 cigarette per day for less than one year) within larger population-based studies were included in the qualitative analysis, but not in the meta-analysis [40,41]. The meta-analysis only included studies that assessed findings in the general population. The search that focused on "bronchiectasis" identified 673 articles. Of 75 potentially relevant studies, only 2 assessed whether a previous episode of TB is associated with the development of bronchiectasis in the general population (Table 1) [42,43].

3.1. Quality assessment

The 9 studies included in the meta-analysis and the 2 sub-group analyses of never smokers are summarized in Table 1. None of the studies had the primary objective of characterizing the association between TB and chronic respiratory disease. Nearly all, however, included self-reported TB or clinical history of TB treatment in covariate analyses. With the exception of the retrospective cohort study by Lee [38], all studies were cross-sectional in design. Consequently, we could not establish the nature of the temporal relationship between the exposure (TB) and the outcome (COPD/bronchiectasis).

Of the COPD studies, most were rated as "Fair" or "Good" by both assessors, representing a low or intermediate risk of bias (Table 2). One study may have had compromised sensitivity to detect COPD, due to the absence of post-bronchodilator spirometry [34]. A few studies suffered from potential selection bias due to low participation rates (<50%), differences between respondents and non-respondents, poor matching between the populations assessed for the exposure (TB) and the outcome (chronic respiratory disease), [34,39] or exclusion of cases diagnosed prior to the commencement of the study [38]. In spite of these limitations, the results were still considered valid for evaluation.

The bronchiectasis studies that were included were considered to be at a higher risk of bias, due to insufficient information provided, non-representative sampling methods, different populations assessed for exposure and outcome, and low participation rates (<50%) [42,43]. However, in the absence of

Table 2
Simplified Quality assessment* of all studies included in the qualitative and quantitative (meta-analysis)

Study Name & Year	Hooper 2012	Perez 2012	Lee 2012	Idolor 2011	Lee 2011	Lamprecht 2011	Caballero 2008	Menezes 2007	Ehrilich 2005	Zhou 2013	Kwak 2010
Study Type:											
C = COPD	C	C	C	C	C	C	C	C	C		
B = Bronchiectasis										B	B
Used for Meta-Analysis:											
Y= Yes	Y		Y	Y	Y		Y	Y	Y	Y	Y
N=No		N				N					
Final Quality	Good							Good			
Assessment		Fair	Fair	Fair	Fair	Fair	Fair		Fair		
										Poor	Poor

* Quality assessment using the National Heart Lung Blood Institute (NHLBI) quality assessment tool for Cohort and Cross sectional studies tool. Overall Quality Assessment Rating;
"Good" - The lowest risk of bias due to study design
"Fair" - Intermediate risk of bias
"Poor" - Risk of bias present (may still be appropriate to use in the absence of other data)

alternative data and given the noted strengths (large sample size for both studies and use of objective computed tomography imaging for one study), the assessors thought it appropriate for them to be included in the meta-analysis. Detailed results using the NHLBI assessment tool are included in the on-line appendix.

3.2. COPD findings

Two population-based cross-sectional studies using the Burden of Obstructive Lung Disease (BOLD) protocol found that a reported history of TB was associated with spirometry-confirmed COPD among people aged 40 years and over (odds ratios (ORs) ranged from 1.78 to 6.31) [33,35]. The strongest association was reported in the Philippines (Table 3) [35]. The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) and the Prevalence of COPD in Colombia (PREPOCOL) projects also demonstrated strong associations between a history of TB and the presence of COPD (ORs 2.33 and 2.94 respectively), in the same age group [36,37]. Importantly, the reported odds ratios have been adjusted for known COPD risk factors, including cigarette smoking and age. In a sub-analysis of never-smokers over the age of 40 years from the PLATINO group [40] the OR for COPD among patients with a history TB compared to those without was even higher (3.7) than the OR for the whole population, despite applying a stricter definition for COPD [44].

The strength of this effect appears to be strongly correlated with the national TB incidence rate. Figure 2 displays odds ratios reported in specific study settings relative to the WHO estimated TB incidence rate for that particular country[4]; for multi-country studies the mean TB incidence of all participating countries was used. In countries with a reported TB incidence of more than 100/100 000 population/year the odds of having COPD were over three times higher among people with a history of TB than among people without such a history (adjusted OR 3.13 for Korean adults; 4.9 and 6.6 for South African males and females respectively and 6.31 for the Philippines) [34,35,39].

The effect of TB on COPD appears to be modified by age. Adults less than 40 years of age were included in only 3 of 7 COPD studies,[34,38,39] since COPD is relatively uncommon among people aged less than 40 years. Whilst two of the studies did not report disaggregated results by age, one study did [38]. The Taiwan study demonstrated that a history of TB was more strongly associated with COPD in adults younger than 40 years of age (HR 4.29; 95% CI 2.62-7.02) than among adults aged 40 years and over (HR 1.94; 95% CI1.65-2.2)[30,31].

Table 3
Results of Included Studies.

COPD Studies	Subjects	Age Group	Limitations	P-value	Odds/Hazard ratio
*Hooper 2012	General population 14 different countries (BOLD)	>40 years	- TB exposure subject to recall bias	0.007	adj. OR: 1.78 (95% CI: 1.17-2.72)
Perez 2012	Never smokers (PLATINO)	>40 years	Subgroup analysis (never smokers only)	0.01	adj. OR: 3.7 (95% CI: 1.4-9.6)
*Lee 2012	Taiwanese	>18 years	- Outcome subject to sensitivity bias (subjects on COPD treatment only) - No adjustment for cigarette smoking	<0.001	HR: 2.054 (95% CI: 1.768–2.387)
	Taiwanese	18-40 years		<0.001	HR: 4.291 (95% CI: 2.623–7.020)
	Taiwanese	>40 years		<0.001	HR: 1.937 (95% CI: 1.653–2.269)
*Idolor 2011	Philippino adults	>40 years	- TB exposure subject to recall bias	<0.0001	adj. OR 6.31 (95% CI: 2.67-15.0)
*Lee 2011	Korean adults	>18 years	- Pre-Bronchodilator COPD detection only - < 50% Participation	<0.001	adj. OR: 3.13 (95% CI: 1.86-5.29)
Lamprecht 2011	Never smokers Male (BOLD)	>40 years	Subgroup analysis (never smokers only)	0.464	adj. OR 1.65 (95% CI: 0.43- 6.34)
	Never smokers Female (BOLD)	>40 years		0.323	adj. OR 1.47 (95% CI: 0.69-3.12)
*Caballero 2008	Colombian adults	>40years	- TB exposure subject to recall bias	0.001	adj. OR: 2.94 (95% CI: 1.58–5.49)
*Menezes 2007	PLATINO	>40years	- TB exposure subject to recall bias	<0.0001	adj. OR: 2.33 (95% CI: 1.50–3.62
*Ehrilich 2004	South African Males	>15 years	- Clinical diagnosis of COPD - Participation rate unreported	<0.05	adj. OR: 4.9 (95% CI: 2.6–9.1)
	South African Females	> 15 years		<0.05	adj. OR: 6.6 (95% CI: 3.7–11.7)
Bronchiectasis studies					
*Zhou 2013	Chinese adults	> 40 years	Clinical diagnosis	<0.05	adj. OR: 3.07 (95% CI: 1.89-4.98)
*Kwak 2010	Korean health screening	> 18 years	- Selection bias possible (Not random simple) - < 50% Participation	0.001	adj. OR: 4.61 (95% CI 2.39-8.88)

* Denotes study used in meta-analysis
OR: Odds ratio
HR: Hazard Ratio
BOLD sites: Adana (Turkey), Cape Town (South Africa), Guangzhou (China), Krakow (Poland), Manila (Philippines), Salzburg (Austria), Hannover (Germany), Bergen (Norway), Lexington (USA), Uppsala (Sweden), London (UK), Reykjavik (Iceland), Sydney (Australia), Vancouver (Canada).
PLATINO sites: Sao Paolo (Brazil), Montevideo (Uruguay), Mexico City (Mexico), Santiago (Chile), Caracas (Venezuela).
"Never Smokers": Have smoked less than 20 packets of cigarettes in their life or less than 1 cigarette per day for less than one year.

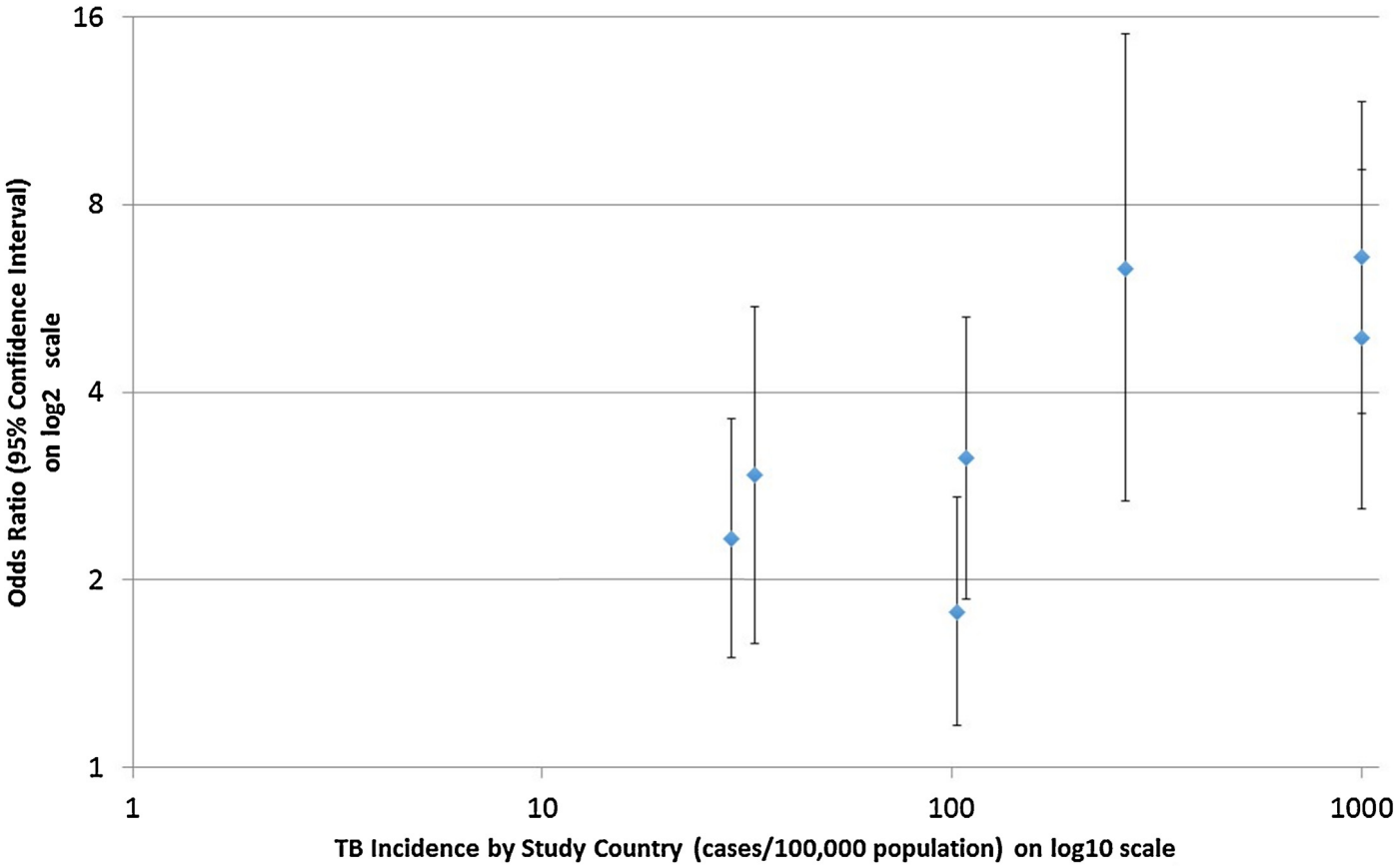

Figure 2. Odds Ratio for COPD in patients with a history of TB, according to the TB incidence in respective study countries.
Study countries included (from highest TB incidence to lowest):
South Africa (Ehrilich 2004), Philippines (Idolor 2011), Republic of Korea (Lee 2011), BOLD countries (Hooper, 2012), Colombia (Caballero, 2008) and PLATINO countries (Menezes, 2007).
For studies with multiple country sites (BOLD and PLATINO), the average incidence was used as described below.
BOLD*: Average 103 per 100,000/year
Australia (6.5), Austria (7.9), Canada (4.6), China (73), Germany (5.6), Iceland (3.5), Norway (7.5), Philippines (265), Poland (21), United Kingdom (15), United States of America (3.6), South Africa (1003), Sweden (7.2), Turkey (22).
PLATINO**: Average 29 per 100,000/year
Brasil (46), Chile 16), Mexico (23), Uruguay (27), Venezuela (33).

3.3. Bronchiectasis findings

The evidence that TB is a risk factor for the subsequent development of bronchiectasis is less robust than for COPD. Only 2 studies, both from eastern Asia, were included. Study findings demonstrated similar and significant positive associations. In a large population-based cross-sectional study of adults aged over 40 years living in urban China (n = 10,811), a history of pulmonary tuberculosis was significantly associated with the medical diagnosis of bronchiectasis (OR 3.07 with 95% CI 1.89-4.98) [42]. Using computed tomography (CT) imaging as the reference standard, a Korean study also demonstrated a significant relationship between previous TB and bronchiectasis (OR 4.61 with 95% CI 2.39-8.88) among healthy adults aged 23-86 years [43].

3.4. Meta-analysis

Figure 3 shows a forest plot of all the included studies and the pooled estimate. The pooled effect estimate was 3.05 (95% confidence interval 2.42 to 3.85; $p < 0.0001$), but there was significant heterogeneity among studies (Cochrane's Q 46.2, $P < 0.0001$, $I^2 = 76\%$). Neither the pooled effect estimate nor the heterogeneity assessment were significantly influenced by the inclusion or exclusion of the two bronchiectasis studies.

4. Discussion

This systematic review and meta-analysis reveals a strong and consistent positive association between a history of tuberculosis and the presence of chronic respiratory diseases (including both COPD and bronchiectasis). The strength of the association showed considerable variation depending on the TB incidence rate within the study setting. The strongest associations between TB and COPD were reported from countries with higher TB incidence rates, such as South Africa and the Philippines (OR ~6) with estimated annual TB incidence rates of 1003 and 265 per 100,000 population respectively. Studies conducted in settings with lower TB incidence rates (<40/100,000 population) reported lower odds ratios (OR ~3). The multisite BOLD study appears to contradict this observation, reporting an OR of 1.78 with mean TB incidence of 103/100,000. However, the mean TB incidence was greatly influenced by a single outlier, South Africa, while most of the 14 sites were located in countries with TB incidence rates below 40/100 000 (except the Philippines and China).

The association between TB and COPD was found to be stronger among younger adults (<40yrs), in studies where this was assessed. This may be explained by the natural history of COPD, which reflects cumulative lung damage that results from environmental exposures and other lung insults. Cigarette

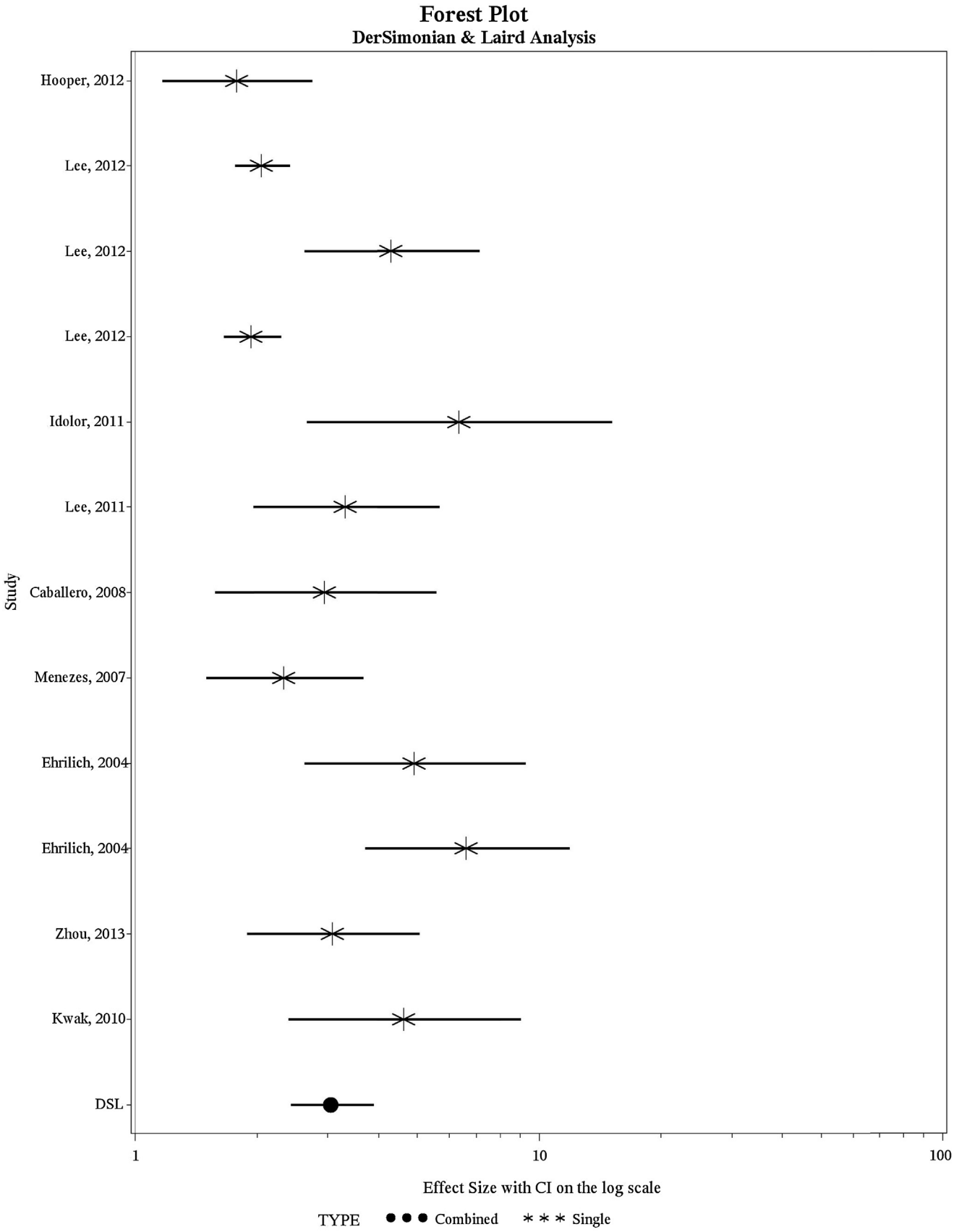

Figure 3. Effect size of a past history of tuberculosis on COPD or Bronchiectasis.

smoking is the dominant risk factor. Since the extent of alveolar destruction and airway obstruction, mediated by both genetic and behavioural factors (such as the depth of inhalation and pattern of smoking) [45] is slowly progressive [46], smoking-related COPD is uncommon in younger people [47]. Pulmonary tuberculosis on the other hand is primarily a disease of young adults [4] and the associated lung damage occurs during the acute disease process, which explains why its relative contribution to COPD is higher in the younger age group, especially in TB endemic areas.

The relationship between TB and COPD in non-smokers is supported by data from the BOLD and PLATINO studies (high and middle income countries) [48,49] that performed sub-group analyses on never-smokers and found even stronger associations between TB and COPD in people who have never smoked [40,41]. Although TB is an established risk factor for obstructive lung function, the phenotype of "TB associated COPD" is often considered to be different from "smoking-related COPD" [33,36,47]. The available evidence suggests that, at least with respect to some important outcomes, the disease has similar manifestations, despite different aetiologies. Several studies demonstrate the persistence of lung function loss, presence of exacerbations as well as the potential for longer term sequelae and respiratory failure in patients with "TB associated COPD",[50–53] similar to "smoking-related COPD".

The fact that the presence of ventilatory restriction, as measured by a reduced forced vital capacity (FVC) is an important predictor of mortality among COPD patients [54] could have implications for TB patients who have combined restrictive and obstructive lung function deficits. This is supported by studies from TB endemic countries such as South Africa, Romania, Pakistan, India, Korea and Brazil that have characterised the patterns of lung function loss that exist among pulmonary TB patients [50,51,55–58]. Abnormal lung function, as measured by spirometry, associated with pulmonary TB was observed in between 18-94% of patients. The extent of the lung function abnormality often correlated with the degree of radiological impairment, number of TB episodes and presence of other respiratory co-morbidities. There was frequently a combination of both restriction and obstruction [50–52].

Bronchiectasis has been regarded as an "orphan" lung disease [59]. We identified only 2 studies assessing the association between TB and bronchiectasis [42,43], although it is known to be common in patients with extensive TB disease since the time of William Osler [60–62]. This may reflect the fact that non-invasive tests to confirm the presence of bronchiectasis (high resolution CT) [63] are relatively new and rarely available in resource-limited settings, where most of the world's TB disease burden is concentrated. Several recent case series from TB endemic countries support this, with prevalence of bronchiectasis observed to be as high as 85% among subjects previously treated for pulmonary TB [64,65]. Among patients presenting with bronchiectasis in Nepal, a past history of TB was the most common cause of bronchiectasis identified [66]. Multiple lung insults results in a greater potential for non-reversible lung injury and not uncommonly a combination of COPD and bronchiectasis.

Strengths of this meta-analysis include the population-based focus, the diversity of study settings, the objective outcome measures used (spirometry or CT in all but 3 studies) and the fact that outcome assessors were blinded to exposure classification. Nearly all studies adjusted for confounding by risk factors such as smoking, biomass fuel exposure and low socio-economic status. Overall methodological quality limited the risk of bias, as judged by the NHLBI quality assessment process [29]. Although there was significant heterogeneity in effect estimates across studies, all effect estimates for the association between TB and COPD or bronchiectasis indicated a positive association.

Study limitations include cross-sectional assessment, which precluded an assessment of temporal relationships. Although TB is likely to contribute to chronic respiratory disease, COPD may be treated with systemic and inhaled corticosteroids, which are known to increase the risk of TB [67–70]. The retrospective cohort study by Lee et al (2012) used a nationwide, universal health insurance database in Taiwan [38]. They were able to establish that no TB patients received COPD treatment in the 3 years prior to their TB episode. This suggests that COPD treatment did not contribute to TB vulnerability and the positive association found reflects TB as a contributing factor to COPD development. Few studies assessed the presence of post-bronchodilator airflow obstruction in people aged less than 40 years, which limits the generalizability of our findings concerning the modification of the effect by age. Although we have combined both odds ratios and hazard ratios in this meta-analysis, we believe this is unlikely to result in any important bias in the estimation of the pooled estimates. Our review did not find any population based studies from low income countries, where TB is likely to be a significant contributor to chronic lung disease.

The findings are important for public health practitioners and policy makers, because of the strength and consistency of the association and the magnitude of the problem. With COPD now the 3rd most common cause of death globally [21], there is an urgent need to prevent the significant number of non-smoking (and smoking) related COPD cases, particularly in TB endemic areas. Reduction in cigarette smoking is essential to reduce the prevalence of COPD in high, middle and low income countries [54]. However, in low income countries up to a third of COPD patients have never smoked [71]. Tuberculosis, on the other hand, is common with 80% of the 9 million new cases this year occurring in low and middle income countries [4,72].

5. Conclusion

The respiratory effects of smoking and its impact on COPD are well known. However, the lung sequelae of pulmonary TB may be a significant contributor to COPD population attributable risk, particularly in TB endemic areas and in younger adults. In addition, increasing rates of cigarette smoking, together with worsening air pollution (indoor and outdoor) will exacerbate the lung damage that results from TB. It demonstrates the need to improve TB control and to link patients to ongoing care after TB treatment completion, but also for comprehensive strategies to improve lung health at the population level.

Conflict of Interest/Funding: None

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2014.12.016.

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